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<p>(54) Title: STABILIZED CATECHOLAMINE SOLUTIONS</p> <p>(57) Abstract</p> <p>The present invention provides a pharmaceutical composition comprising a catecholamine and a metal ion chelator admixed in an aqueous solution adjusted to a pH value of about 1.5 to about 4.0. The catecholamine is preferably dobutamine, the metal ion chelator is selected from the group consisting of EDTA, EGTA, edetic acid and diethylenetriaminepentaacetic acid, and the pH is preferably about 2.5. The present invention further provides a method for increasing cardiac contractility in a warm-blooded animal in need of such treatment comprising administering to said animal an effective amount of a catecholamine and a metal ion chelator admixed in an aqueous solution adjusted to a pH value of about 1.5 to about 4.0.</p>		

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STABILIZED CATECHOLAMINE SOLUTIONS

DescriptionTechnical Field of the Invention

The present invention relates to catecholamine solutions stabilized by the addition of metal ion chelators and adjustment of pH and the use of such solutions to increase cardiac contractility.

Background of the Invention

Catecholamines are hormones of the sympathetic nervous system. Chemically, catecholamines are amine derivatives of catechol (2-hydroxyphenol). The three best known naturally occurring catecholamines are epinephrine (adrenaline), norepinephrine (noradrenaline) and dopamine. Synthetic catecholamines include dobutamine and isoproterenol.

As a class, catecholamines have cardiovascular effects that form the basis for their therapeutic usefulness. Injection of epinephrine in humans leads to rapid increases in systolic blood pressure, heart rate, cardiac output and respiration, and causes a decrease in peripheral resistance. Epinephrine also increases cardiac arrhythmias. Clinically, epinephrine is used to treat certain types of shock, especially anaphylactic shock.

Injection of norepinephrine increases peripheral resistance while decreasing heart rate and cardiac output, while nevertheless increasing systolic and diastolic blood pressure. Norepinephrine also increases cardiac arrhythmias. Clinically, the bitartrate salt is used to treat certain acute hypotensive states, such as occur during myocardial infarction and septicemia.

Dopamine is the immediate metabolic precursor of both epinephrine and norepinephrine. Dopamine, when

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administered to humans, has a positive inotropic effect on myocardial tissue. Dopamine usually has no effect on peripheral resistance. As a therapeutic agent, dopamine is used to treat certain types of shock, as well as chronic congestive heart failure.

Dobutamine, disclosed in United States Patent No. 3,987,200 to Tuttle et al., is a dopamine derivative which also has a positive inotropic effect, but has minimal effects on blood pressure and does not induce arrhythmias. Dobutamine is used clinically in the short-term treatment of organic heart disease or decreased cardiac contractility following cardiac surgery.

A variety of dobutamine analogues have also been disclosed. For example, United States Patent No. 4,704,407 to Massey relates to soluble salts of dobutamine formed with hydroxy alkanoic, polyhydroxy alkanoic, hydroxalkandioic and polyhydroxyalkandioic acids (e.g. lactic acid, gluconic acid, lactobionic acid, glucoheptonic acid, glyceric acid, glycollic acid, tartaric acid, malic acid, mevalonic acid, dihydroxybutyric acid, dihydroxyvaleric acid, erythronic acid, bis(hydroxymethyl) malonic or acetic acids, dihydroxyadipic acid, and the like).

Su et al., United States Patent No. 4,581,225 discloses dobutamine salts of phosphoric, sulfuric, hydrobromic, and hydrochloric acids. The patent also discloses an intranasal sustained release formula comprising a catecholamine, an emulsifying agent, both suspended in a freon aerosol propellant, and a sustained release agent which is a derivative of oleic acid.

Bodor et al., United States Patent No. 4,340,603 discloses novel prodrug derivatives of

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dobutamine. These compounds are said to increase bioavailability.

Diamond, United States Patent No. 4,663,351, relates to a novel prodrug derivative of dobutamine, specifically a tri-isobutyric acid ester or pharmaceutically acceptable salt thereof.

Tuttle, United States Patent No. 4,562,206, discloses a novel catecholamine useful for increasing cardiac contractility. The novel compound is a diisobutyrate derivative of dobutamine.

Isoproterenol has prominent cardiovascular and smooth muscle effects. Intravenous administration of isoproterenol leads to lower peripheral resistance with a concomitant increase in cardiac output and an overall decrease in mean blood pressure. Clinically, isoproterenol injection is used for heart block, Adams-Stokes attacks, and acute bronchospasm.

Catecholamines in solution oxidize in the presence of atmospheric oxygen. In order to increase the shelf-life of these solutions, antioxidants are used. Currently, all known commercial injectable catecholamine solutions use sodium bisulfite or sodium metabisulfite as antioxidants. Many people are allergic to ingestion of sulfites such as these, with symptoms including severe headaches, tachycardia and difficulty breathing. This allergic reaction is commonly known as "salad bar syndrome," as sulfites are commonly used in restaurant salad bars to keep salad greens from turning brown as a result of oxidation.

The presence of sulfites in injectable solutions of catecholamines thus presents problems when administering these solutions to patients who are allergic. Indeed, the symptoms of an allergic reaction to sulfites may exacerbate the condition being treated by the catecholamines. This exacerbation is especially

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critical given that catecholamines are often used in emergency situations where further compromising a patient with an allergic reaction is disadvantageous.

The present invention overcomes the limitations of currently used catecholamine solutions by stabilizing solutions of catecholamines by adjusting the pH value of those solutions and by adding a metal ion chelator.

Summary of the Invention

The present invention provides a pharmaceutical composition comprising a catecholamine and a metal ion chelator admixed in an aqueous solution adjusted to a pH value of about 1.5 to about 4.0. A preferred catecholamine is dobutamine. Preferred metal ion chelators are selected from the group consisting of ethylenediaminetetraacetic acid (EDTA), edetic acid, ethylene glycol-bis(β -aminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA) and diethylenetriaminepentaacetic acid and salts and/or hydrates of these acids. A particularly preferred metal ion chelator is EDTA. A preferred pH value is about 2.5.

The present invention also provides a method for increasing cardiac contractility in a warm-blooded animal in need of such treatment comprising administering to said animal an effective amount of a catecholamine and a metal ion chelator admixed in an aqueous solution adjusted to a pH value of about 1.5 to about 4.0. This aqueous solution is identical to that set forth above as a pharmaceutical composition.

Detailed Description of the Invention

The present invention provides for prevention of oxidation of catecholamines in solution, thus maintaining adequate shelf-life, while avoiding the

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complications of sulfite allergy potentially present in all currently used solutions of catecholamines.

The present invention also provides for a method of increasing cardiac contractility in mammals by administering to mammals in need of such treatment an effective amount of a catecholamine and a metal ion chelator admixed in a solution whose pH has been adjusted to an appropriate value.

One aspect of the present invention involves a pharmaceutical composition comprising a catecholamine and a metal ion chelator admixed in an aqueous solution adjusted to a pH value of about 1.5 to about 4.0.

The structure and function of catecholamines are discussed elsewhere herein. Preferred catecholamines useful in the present invention are selected from the group consisting of epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine, dobutamine and isoproterenol. A particularly preferred catecholamine is dobutamine.

As used herein, "metal ion chelator" refers to a compound which will coordinate with a metal ion such as Co^{2+} , Ni^{2+} , Cu^{2+} , Mg^{2+} , Mn^{2+} or Zn^{2+} . These metal ion chelators may be used as free acids, salts and/or hydrates. Exemplary metal ion chelators include ethylenediamine tetraacetic acid (EDTA), the cupric disodium salt of EDTA, the disodium dihydrate of EDTA, the trisodium salt of EDTA, the tetrasodium hydrate of EDTA, the dipotassium salt of EDTA, the disodium-calcium salt of EDTA, the ferric-sodium salt of EDTA, edetic acid, ethylene glycol-bis-(β -amino ethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), diethylenetriamine-pentaacetic acid, nitriloacetic acid, the disodium salt of nitroloacetic acid, and the trisodium salt of nitriloacetic acid. Preferred metal ion chelators include ethylenediaminetetraacetic acid (EDTA), edetic

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acid, ethylene glycol-bis(β -aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), diethylenetriaminepentaacetic acid and nitriloacetic acid. A particularly preferred metal ion chelator is EDTA. Preferred metal ion chelators may be used as a free acid, salt and/or hydrate.

The metal ion chelator is present in the composition of the present invention in an amount sufficient to chelate any metal ions present. As this is a stoichiometric reaction, an amount of metal ion chelator in excess of the amount of metal ions present is typically used. A preferred amount of a metal ion chelator is from about 1 milligram per milliliter to about 0.01 milligrams per milliliter. A more preferred amount of a metal ion chelator is from about 0.5 to about 0.1 milligram per milliliter.

The catecholamine is present in the composition of the present invention in an amount sufficient to have the desired pharmacological effects. The catecholamine may also be present in a concentrated amount, to be subsequently diluted prior to use. A preferred amount of a catecholamine is from about 15 to about 0.15 milligrams per milliliter. A more preferred amount is from about 12.5 to about 1 milligrams per milliliter. A still more preferred amount is from about 5 to about 1.0 milligram per milliliter.

The pH value of an aqueous solution can be adjusted by the judicious addition to that solution of either an acid or a base. If the aqueous solution has a pH value higher than the desired pH value, then the pH value is adjusted by the addition of an appropriate acid (e.g. hydrochloric acid). Conversely, if the aqueous solution has a pH value lower than the desired pH value, then the pH value is adjusted by the addition of an appropriate base (e.g. sodium hydroxide).

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The pH value of the aqueous solution of the present invention is adjusted to a pH value of about 1.5 to about 4.0. A preferred pH value of that aqueous solution is about 2.5.

In another aspect, the present invention relates to a method for increasing cardiac contractility in a warm-blooded animal in need of such treatment comprising administering to that animal an effective amount of a catecholamine and a metal ion chelator admixed in an aqueous solution adjusted to a pH value of about 1.5 to about 4.0.

As used herein, "increasing cardiac contractility" refers to an increase in cardiac function by exerting a positive inotropic effect. Catecholamines increase cardiac contractility through such a mechanism.

A variety of cardiovascular diseases benefit from increased cardiac contractility. Most notable is congestive heart failure, a common sequela to atherosclerosis. Likewise, cardiogenic shock, a frequent cause of death, can be treated by increasing cardiac contractility. Indeed, decreases in cardiac contractility resulting from organic heart disease or surgical procedures benefit from inotropic support.

As used herein, "an effective amount" means that amount of a compound having cardiac contractility increasing activity which when administered to a mammal is sufficient to provide a positive inotropic effect. The particular amount for a given compound will vary with numerous factors including route of administration, sex of the mammal, body weight and the like.

The present invention can use one or more of the compounds used in this invention formulated into compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants or vehicles which are collectively referred to herein as

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carriers, for parenteral injection (i.e. intravenously, intramuscularly or subcutaneously.)

Compositions suitable for parenteral injection can comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions can also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

If desired, and for more effective distribution, the compounds can be incorporated into slow release or targeted delivery systems such as polymer matrices, liposomes, and microspheres. They may be sterilized, for example, by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or

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some other sterile injectable medium immediately before use.

Actual dosage levels of active ingredient in the compositions of the present invention may be varied so as to obtain an amount of active ingredient that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, on the route of administration, on the desired duration of treatment and other factors.

The total daily dose of the compounds of this invention administered to a host in single or divided doses may be in amounts, for example, of from about 2.5 to about 40 micrograms per kilogram of body weight per minute. Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular subject will depend upon a variety of factors including the body weight, general health, sex, diet, time and route of administration, rates of absorption and excretion, combination with other drugs and the severity of the particular disease being treated.

The following examples further illustrates the invention and is not to be construed as limiting of the specification and claims in any way.

Example 1 pH Effects on Dobutamine Solutions
 Containing Sodium Metabisulfite

An aqueous admixture containing 0.5 milligrams per milliliter of dobutamine (HCl), 4.5 percent dextrose monohydrate, 0.25 milligrams per milliliter of sodium metabisulfite, and 0.1 milligrams per milliliter of disodium EDTA was prepared. The pH of the admixture was

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adjusted to a value of 3.5 with 1 normal (N) hydrochloric acid (HCl) and aliquoted into solutions A, B, C and D indicated in Table 1. The pH of the admixture was further adjusted to a value of 3.0 with 1N HCl, and aliquoted into solutions E and F indicated in Table 1. The pH of the admixture was adjusted to a final value of 2.5 with 1N HCl, and aliquoted into solutions G, H, I and J indicated in Table 1.

Each of the solutions was placed into polyester containers (referred to as dosage forms) of equal surface area. The amount of solution in each bag is listed as the Fill Volume in Table 1. Each solution was then autoclaved. The pH value of each solution was obtained after autoclaving. These values are listed under the column headed "Measured pH" in Table 1. Percentage values of dobutamine and sodium metabisulfite (Na metabisulfite) were also obtained. Oxidation of dobutamine was monitored by observing changes in coloration.

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Table 1

Solution	Fill Volume (ml)	Dobutamine %	NaMetabi- sulfite %	F ₂	Measured pH
A	50	99.0	56	8	3.21
B	50	99.0	44	16	3.50
C	100	99.6	60	8	3.54
D	100	100.2	56	16	3.50
E	100	99.2	56	8	3.01
F	100	99.6	52	16	--
G	50	100.8	36	8	2.65
H	50	100.4	28	16	2.62
I	100	100.0	44	8	2.55
J	100	99.6	40	16	2.59

 *Heat input of sterilization

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A control solution adjusted to a pH value of 3.5 was placed in a dosage unit and assayed prior to autoclaving, and was found to have a pH value of 3.55 and 100.0% dobutamine.

With respect to coloration, a larger F_0 value had a slight effect. The greatest effect was that of pH value. As pH value increased, so did coloration. This result indicates that lower pH values prevent the degradation of dobutamine. The dobutamine degradation products, alone or in combination with other factors, leads to color formation.

Example 2 pH Effects on Dobutamine Solutions
 Containing Sodium Metabisulfite

An aqueous admixture containing 2.24 milligrams per milliliter of dobutamine HCl, 5.0 percent dextrose monohydrate, 0.25 milligrams per milliliter of sodium metabisulfite, and 0.1 milligrams per milliliter of disodium EDTA was prepared. The pH of the admixture was adjusted to a value of 3.5 with 1 normal (N) HCl and aliquoted into solutions A, B, C and D indicated in Table 2. The pH of the admixture was further adjusted to a value of 3.0 with 1N HCl, and aliquoted into solution E indicated in Table 2. The pH of the admixture was adjusted to a final value of 2.5 with 1N HCl, and aliquoted into solutions G, H, I and J indicated in Table 2.

Each of the solutions was placed into 100 ml polyester bags. The amount of solution in each bag is listed as the Fill Volume in Table 2. Each solution was then autoclaved. The pH value of each solution was obtained after autoclaving. These values are listed under the column headed "Measured pH" in Table 2. Percentage values of dobutamine and sodium metabisulfite (Na metabisulfite) were also obtained. These percentage

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values reflect the percentage of the theoretical concentration of free dobutamine remaining. Oxidation of dobutamine was determined by observing changes in coloration.

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Table 2

Solution	Fill Volume (ml)	Dobutamine %	Na Metabi- sulfite %	F ₀ *	Measured pH
A	50	101.5	60	8	3.42
B	50	99.8	44	16	3.38
C	100	101.6	60	8	3.44
D	100	100.8	60	16	3.44
E	100	99.1	56	16	3.04
G	50	101.6	40	8	2.53
H	50	102.0	32	16	2.56
I	100	101.2	52	8	2.50
J	100	101.0	48	16	2.52

* Heat input of sterilization

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A control solution adjusted to a pH value of 3.5 was placed in a dosage form and assayed prior to autoclaving, and was found to have a pH value of 3.49 and 101.6% dobutamine.

With respect to coloration, the results are essentially the same as discussed in Example 1. Once again, the greatest effect was that of pH value. As pH value increased, so did coloration. This result indicates that lower pH values prevent the degradation of dobutamine.

Example 3 Effects of Disodium EDTA, pH and Headspace Oxygen on Coloration

Two separate lots of aqueous dobutamine-containing admixtures were prepared. In Lot 1, the admixtures contained 2.24 milligrams per milliliter of dobutamine HCl and 5 percent weight to volume of dextrose monohydrate. In Lot 2, the admixtures contained 2.24 milligrams per milliliter dobutamine HCl, 5 percent weight to volume dextrose monohydrate, and 0.3 milligrams per milliliter disodium EDTA dihydrate.

The pH value of aliquots of these two lots was adjusted with 1N HCl. The headspace oxygen was adjusted by gassing the solution with nitrogen gas after filling the ampule, and was determined by checking headspace oxygen levels at the beginning, middle and end of the filling of each lot of ampules. A Mocon Headspace Oxygen Analyzer was used for these determinations.

The American Public Health Administration (APHA) color was determined subjectively, according to standard procedures. Since this method did not, in all cases, lead to a satisfactory reading (as the hues of these solutions did not match the APHA color standards), this test method was abandoned. For each lot of ampules

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prepared, samples were placed at 5°C for comparison with samples stored at 60°C, 40°C and 25°C.

Table 3

Solution	Headspace Gassing*	pH	APHA Color	Rank within pH Group**
Lot 1				
A	<1%	2.55	~15	1
B	10-13%	2.55	~100	2
C	atmos***	2.55	>100	3
D	<1%	1.58		1
E	10-13%	1.58		2
F	atmos***	1.58		3
Lot 2				
A	<1%	2.50		1
B	10-13%	2.50		1
C	atmos***	2.50		1
D	<1%	1.53		1
E	10-13%	1.53		1
F	atmos***	1.53		1

* Indicates approximate levels of oxygen in the headspace.

**Indicates the relative color ranking within a group of solutions with equal pH values. Group I consists of Lot 1, solutions A, B and C; Group II consists of Lot 1, solutions D, E and F; Group III consists of Lot 2, solutions A, B and C; and Group IV consists of Lot 2, solutions D, E and F. Both Lot 2 groups (Groups III and IV) had equivalent colors, corresponding to the color of solution D of Lot 1.

*** Indicates atmospheric oxygen levels.

On average, the solutions of Lot 2 had lower APHA color readings than the solutions of Lot 1. The lower color readings are indicative of decreased amounts of dobutamine degradation. The data support the contention that lower pH, coupled with the inclusion of the metal ion chelator EDTA, leads to a reduction in the amount of catecholamine degradation. This result is

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true even in the complete absence of sodium metabisulfite in any of the assayed solutions.

Example 4 Stability of EDTA-Containing, pH Adjusted Dobutamine Solutions

The solutions prepared in Example 3 were kept for 2 weeks at a temperature of 60°C. At the end of that period, the solutions were evaluated for coloration. The solutions of Group I showed significant particulate matter in the solutions. The solutions of Group II were darker than those of Group I. The solutions of Group III showed the best overall colors (i.e., the least coloration) of all of the groups. The solutions of Group IV were slightly darker than Group III, but were lighter in color than the solutions of either Group I or Group II.

Overall, solution A of Lot 2 exhibited the least color. This solution had a headspace oxygen level of less than 1 percent, a pH value of 2.5, and contained disodium EDTA to 0.3 milligrams per milliliter.

Example 5 Effects of pH and Headspace Oxygen on Degradation of Dobutamine

An aqueous admixture containing 5 percent (weight to volume) of dextrose monohydrate, dobutamine HCl equivalent to 2 milligrams per milliliter dobutamine free base, and 0.3 milligrams per milliliter of disodium EDTA dihydrate was prepared. Headspace oxygen levels were adjusted to less than 1% by gassing with nitrogen gas, or left at atmospheric levels. The pH value of solutions A and B of Table 4 was left unchanged. The pH value of solutions C and D was adjusted by the addition of sodium hydroxide (NaOH).

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Table 4

Solution	pH	Headspace Oxygen	Coloration
A	4.87	atmos*	Very pale pink
B	4.87	<1%	Nearly colorless
C	5.73	atmos*	Definitely yellow
D	5.73	<1%	Pinkish

* Indicates atmospheric oxygen levels.

Pink coloration indicates very slight degradation of dobutamine in the solution. Pink coloration was observed in solutions wherein protection from excessive oxygen levels by gassing the solutions with nitrogen was not employed. Because of availability of oxygen and higher pH value, solution C had degraded more quickly and to a greater extent than solutions A, B, and D.

Example 6 Stability of EDTA-Containing, pH Adjusted
 Dobutamine Solutions

The solutions prepared in Example 3 were maintained at room temperature for a period of three months. At the end of that time period, the pH value and coloration of each solution was determined. The results are shown in Table 5.

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Table 5

Solution	Headspace Gassing*	pH	Color Observation
Lot 1			
A	<1%	2.6	Slight straw
B	10-13%	2.6	Brown/gray
C	atmos**	2.6	Gray
D	<1%	1.6	Slight straw
E	10-13%	1.6	Yellow
F	atmos**	1.6	Yellow
Lot 2			
A	<1%	2.5	Colorless
B	10-13%	2.5	Colorless
C	atmos**	2.6	Colorless
D	<1%	1.6	Slight straw
E	10-13%	1.6	Straw
F	atmos**	1.6	Yellow/brown

*Indicates approximate levels of oxygen in the headspace.

**Indicates atmospheric oxygen levels.

Solution C of Lot 2 indicates that the presence of disodium EDTA maintains the stability of dobutamine solutions even in the presence of atmospheric levels of oxygen. This is accomplished without the use of sodium metabisulfite. This stability is maintained for three months without special storage conditions, and indicates that the presence of a metal ion chelator such as EDTA, coupled with a judicious choice of pH value for the solution, provides protection from degradation of a solution of dobutamine.

Example 7 Stability of EDTA-Containing Dobutamine Solutions

The solutions prepared in Example 5 were examined after 4 weeks at a storage temperature of 4°C. The results are shown in Table 6.

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Table 6

Solution	pH	Headspace Oxygen	Coloration
A	4.2	atmos*	Pinkish/amber
B	4.4	<1%	Slight amber
C	5.2	atmos*	Yellow
D	4.3	<1%	Light Brown

*Indicates atmospheric oxygen levels.

These results indicate that higher pH values lead to greater degradation of dobutamine solutions even at storage temperatures designed to minimize degradation, and even under conditions where headspace oxygen is reduced to less than 1 percent. These data reinforce the importance of providing a sufficiently low pH value for the solution in order to provide for long term stability of the dobutamine solutions.

The foregoing specification, including the specific embodiments and example, is intended to be illustrative of the present invention and is not to be taken as limiting. Numerous other variations and modifications can be effected without departing from the true spirit and scope of the present invention.

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WE CLAIM:

1. A pharmaceutical composition comprising a catecholamine and a metal ion chelator admixed in an aqueous solution adjusted to a pH value of about 1.5 to about 4.0.
2. The composition of claim 1 wherein said catecholamine is dobutamine.
3. The composition of claim 1 wherein said metal ion chelator is selected from the group consisting of EDTA, EGTA, edetic acid and diethylenetriaminepentaacetic acid.
4. The composition of claim 1 wherein said pH value is about 2.5.
5. A method for increasing cardiac contractility in a warm-blooded animal in need of such treatment comprising administering to said animal an effective amount of a catecholamine and a metal ion chelator admixed in an aqueous solution adjusted to a pH value of about 1.5 to about 4.0.
6. The method of claim 5 wherein said catecholamine is dobutamine.
7. The method of claim 5 wherein said metal ion chelator is selected from the group consisting of EDTA, EGTA, edetic acid and diethylenetriaminepentaacetic acid.
8. The method of claim 5 wherein said pH value is about 2.5.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/11511

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/135, 31/195

US CL :514/654,653,566

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/654,653,566

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 3,987,200 (TUTTLE ET AL) 19 OCTOBER 1976, see the claims in particular.	1-8
Y	Chemical Abstracts, Volume 117, No. 10, issued 07 September 1992, Grubstein et al, "Stabilization of epinephrine in a local anesthetic injectable solution using reduced levels of sodium metabisulfite and EDTA" see page 465, column 1, abstract no. 97259m, Drug Dev. Ind. Pharm. 18(14), 1549-1566.	1-8
Y	Chemical Abstracts, Volume 96, No. 18, issued 03 May 1982, Raether et al, "Stabilizing pharmaceutical preparations with oxidation-sensitive constituents", see page 425, column 2, abstract no. 149196h, Ger. (East) DD 150,694.	1-8

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* "A" "E" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be part of particular relevance earlier document published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"T" "X" "Y" "A"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
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Date of the actual completion of the international search

28 January 1994

Date of mailing of the international search report

MAR 03 1994

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/11511

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Biological Abstracts, Volume 74, No. 2, issued 15 July 1982, Heikkila et al, "Inhibition of iron-stimulated catecholamine degradation by the iron chelators Detapac [diethylenetriaminepentaacetic acid] and Desferal: Potentially useful laboratory agents" see page 1468, column 2, abstract no. 14149, Biochem. Pharmacol. 30(21), 2945-2948.	1-8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/11511

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN(CAS, BIOSIS)

search terms: catecholamine, dobutamine, epinephrine, metal chelator, EDTA, EGTA, DTPA, oxidation, degradation, antioxidant, stabilization